Severity of Baseline Pain and Degree of Analgesia in the Third Molar Post-Extraction Dental Pain Model

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The purpose of this study was to determine whether different levels of pain would respond similarly to analgesia. We compared the analgesic response to ibuprofen in subjects with moderate versus severe baseline pain in clinical trials using the third molar post-extraction dental pain model. We performed a pooled raw data analysis of 517 subjects included in the ibuprofen treatment arm of 11 similar studies submitted to the Food and Drug Administration. The inclusion and exclusion criteria were similar in all studies. All studies used the same metrics and recorded pain at the same times. As expected, the well established analgesic effect of ibuprofen was confirmed. More intense baseline pain was initially associated with a larger decrease and greater fractional decreasing in pain intensity after medication. A larger percentage of those with milder baseline pain obtained relief compared with those with severe baseline pain. Reduction in pain intensity occurred mainly in the first 2 h. At later time points, the association of baseline conditions with a reduction in pain level diminished. We conclude that the intensity of initial pain is not correlated with the need for larger doses of analgesic.

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There are some supportive data in the literature indicating that an intense degree of initial pain will result in better response to analgesia treatment in patients with burns (1) and after Caesarean delivery (2). The third molar post-extraction dental pain setting is the most widely used model in acute analgesia clinical trials. This pain model's reproducibility has been well established, and sponsors routinely use it to support analgesia claims in new drug applications submitted to the Food and Drug Administration (FDA). Baseline pain intensity is related in some degree to increased analgesic effect in subjects after third molar surgical extraction by one report (3) but not by another (4). On the average, after a third molar surgical extraction, 60% of subjects will experience moderate pain and 40% will experience severe pain before requesting an analgesic drug (3).

In a previous exploratory work, we compared the analgesia response to ibuprofen in two third molar post-extraction dental pain studies that differed in initial pain level and found that more intense baseline pain was associated with a better analgesic response (5). Fewer subjects were used in that study. To further explore the relationship between baseline pain and response to analgesia, namely changes in categorical pain scores from baseline and the number of patients who achieve relief based on initial pain scores, we did a pooled raw data analysis of all third molar post-extraction dental pain studies recently submitted to the FDA that included an ibuprofen treatment arm. All of the studies had the same standard double-blinded, placebo-controlled, parallel-group design using a single dose of ibuprofen 400 mg as the active comparator.

Materials and Methods

We screened analgesic studies recently submitted to the FDA Division of Analgesic, Antiinflammatory, and Ophthalmic Drug Products that included efficacy data. To be eligible for inclusion in our analysis, studies had to be randomized, including active comparator ibuprofen arms using the third molar post-extraction dental pain model. We performed a meta-analysis of 527 subjects included in the ibuprofen 400-mg treatment arms of 11 double-blinded trials. The study design was similar for all studies and was approved by

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the responsible IRBs. Eligible subjects were otherwise healthy men or nonpregnant women older than 16 yr of age. All subjects selected had to be scheduled to have third molars removed, at least one of which was partially embedded in bone and was a mandibular impaction. Subjects must have been experiencing moderate to severe pain after the procedure (see below for metrics). Subjects were excluded if they used any analgesic within 24 h before taking the study medication or if they had a recent history of chronic analgesic use. Subjects who were obese also were excluded from the study.

Efficacy end-points were pain intensity scores measured by a 4-point categorical scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe) and pain relief scores measured by a 5-point categorical scale (none = 0 and complete = 4). These scores were recorded just before the drug administration and at least at 0.5, 1, 1.5, 2, 3, 4, 5, and 6 h after the dose.

Rescue analgesic medication was allowed, but once a subject received a rescue medication, the time of this event was recorded, and the subject had to be excluded from further pain measurements.

The statistical analysis plan was to combine the raw data of all eligible studies and to analyze the results observed in all randomized patients in the ibuprofen arm. The question to be addressed was whether a comparison over time by baseline pain of the entire set of pain intensity scores and pain relief scores would reveal a systematic difference. Baseline pain intensity measure had only two categories: moderate and severe. Although the pain scores were recorded as categorical values, experience has shown that the outcome over time is most easily perceived in terms of group averages. Scores grouped by baseline pain were to be averaged and displayed as a function of time for visual inspection. At each recorded time, JMP (a statistical software package produced by the SAS corporation, Cary, NC) was used to test for the significance of any difference between the two categories. The Pearson χ^2 test for categorical data was used at each time point to test for significance. We anticipated a larger number of pain intensity score categories at the subsequent postmedication time points (to include none and mild), leading to a smaller count in some cells and potentially casting doubts on the results. For this reason, *t*-test values and nonparametric comparison of pairs were used to check on the robustness of the significance results. Results were consistent in all cases.

Results

Three-hundred-twenty-seven subjects indicating moderate and 190 subjects indicating severe pain (where 0 = none, 1 = mild, 2 = moderate, and 3 = severe) after a surgical extraction of two or more third molars were included in the analysis. Age, sex, and baseline pain distributions for the two categories are shown in Table 1. More than 90% of participants were white. There is no concern regarding the unequal sex ratio because it has been shown that there is no difference between men and women with regard to response to analgesia (6).

The use of pain intensity scores is one of the standard procedures in new drug applications to the FDA for an analgesic indication. In the data we analyzed, pain intensity scores over time for the two baseline treatment groups (Fig. 1) tended to converge from 2 h after medication onward. All subjects were treated with ibuprofen 400 mg.

However, there is an inherent catch in using such a measure to determine efficacy. Subjects with initial more intense pain can achieve larger reductions than subjects with initial less intense pain. For a comparative exploratory analysis, we defined fractional pain intensity scores as the pain intensity score divided by the baseline pain intensity. This definition provides a measure of the degree of treatment effect size achieved for each baseline. Plotting the fractional pain intensity scores over time after medication demonstrates that subjects with more intense baseline pain had more rapid decreases in fractional pain intensity (Fig. 2). By this measure, subjects with more intense baseline pain achieved a larger treatment effect from the start to the end of the study period. The need for additional analgesic medication was similar for subjects who entered the study with moderate or severe pain (Fig. 3). The fraction of those not re-medicated was smaller at some time points for those with more severe baseline pain. For subjects who choose to re-medicate, pain intensity and fractional pain intensity were undefined. They were therefore placed in a separate re-medicate category. Note that in normalizing the pain intensity and considering the fractional reduction, the absolute level of pain is masked.

A different picture is obtained if we ask for the pain state that each fraction of the population is in at a given time. Use of the fraction in each state enables us to compare unequal populations. We created a summary graph for each initial state by combining subsequent pain states. To do so, states of pain 2 and 3 were grouped as a painful state, states 0 and 1 were grouped as relief state, and state "d" stands for re-medication. The results show the pain profile versus time for the entire population (Fig. 4). This is a normalized count graph for pain states by initial condition (IC). It represents the relative frequency of subjects in a given state. For the early period (<2 h), clearly a larger proportion of those with baseline pain 2 left the painful group and entered the relief group. This is reasonable because those initially with pain states 3 most likely first

Table 1. Patient Characteristics

	Moderate baseline pain $n = 327$	Severe baseline pain $n = 190$
Baseline pain	2	3
Age ± SD (range)	22 ± 5 (15 ± 50)	22 ± 4 (15 ± 43)
Sex (F/M)	192/135	133/57

All patients treated with a single dose of ibuprofen 400 mg.

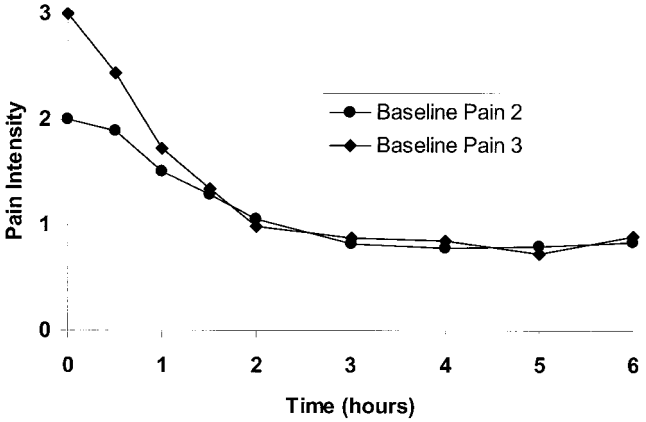

Figure 1. Pain intensity scores over time after medication for subjects with moderate or severe baseline pain.

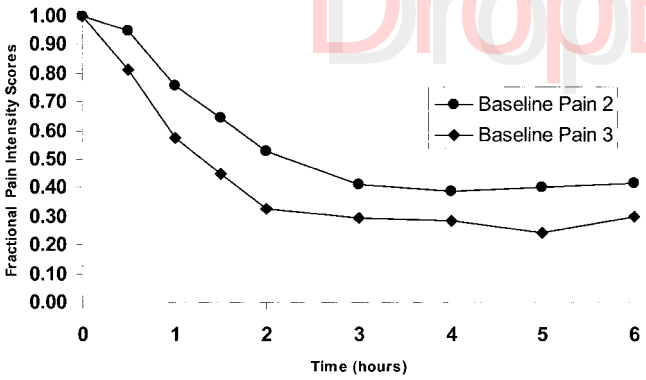

Figure 2. Fractional pain intensity scores over time after medication for subjects with moderate or severe baseline pain.

traverse pain state 2 before obtaining relief. After 1.5 h, the difference in the fraction of patients in either initial pain state who have obtained relief remains small. The distribution from 2 h onward among the different IC states is fairly similar. For the different ICs, there is near convergence of the fractions of patients with relief. Similarly, there is near convergence of the fractions of patients with pain (Fig. 4). This means that a larger percentage of those starting with IC3 got more relief. However, the graph consistently shows that a larger proportion of those who started in state 2 have relief. The graph shows an increased likelihood of relief with

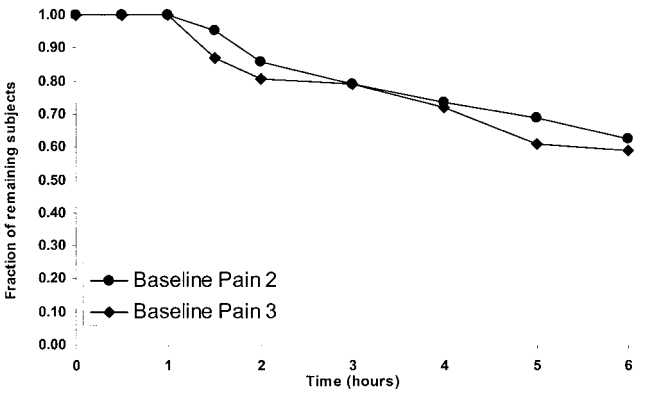

Figure 3. Non–re-medicating participants over time after medication for subjects with moderate or severe baseline pain.

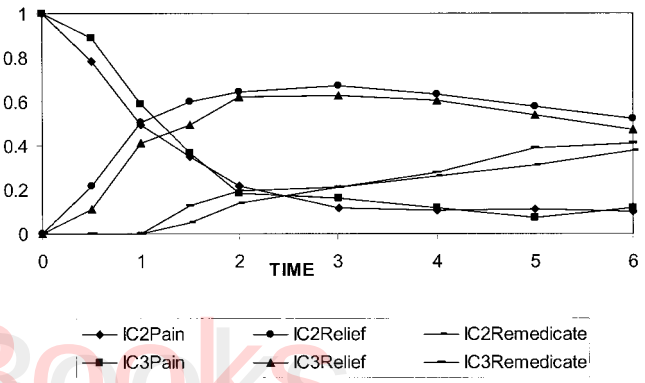

Figure 4. Pain profile. Demonstrates the fraction of population in each pain state by initial condition (IC).

IC2 because for IC3, there are a larger number of re-medicators. Conversely, for most data points, a larger proportion of those who started in pain state 3 have moved to re-medicate. Pain intensity status is clinically significant. Are these average differences statistically significant? A series of Pearson and likelihood ratio tests were performed at each time point. Results are shown in Table 2. Table 2 indicates significance (<0.05) of the difference in pain intensity at each given time because of the IC by showing probabilities of obtaining a χ^2 value larger than that calculated for the given time.

Starting at 30 min, there is a significant difference for initial state. This difference remains significant through 1 h. If we refer to Figure 1, we can clearly see the difference caused by initial states through the first hour. However, although the figure shows that a larger fraction of those with less initial pain obtain alleviation, this consistent difference was not found to be significant from 2 h onward.

Another informative way of looking at the data is to look at the proportions of completers (Fig. 5). At time 0, there is a split of 60%/40% between pain states 2 and 3. At 30 min, we already see major relief because the most painful state is reduced to approximately

Table 2. *P* Values From χ^2 Test Given Versus Time

Test per time	0.5	1	2	3	4	5	6
Likelihood ratio	0.00	0.03	0.26	0.36	0.81	0.12	0.55
Pearson	0.00	0.03	0.26	0.36	0.81	0.13	0.55

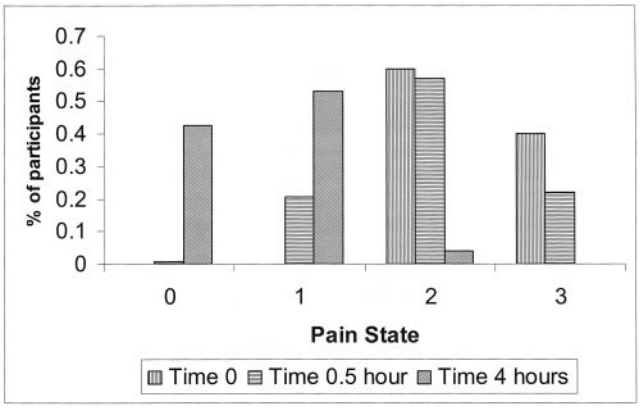

Figure 5. Fraction of completers in pain states 2 (moderate) and 3 (severe).

25%, and the relief state is at 20%. Pain state 2 is almost the same because of the reason explained above, namely those from 3 go to 2 (as those from 2 go to 1). At 4 h, almost all of those who will complete the full 6 h have partial or full relief.

Discussion

Thirty-seven years ago, Lasagna (7) noted that initial pain intensity was important in the assessment of analgesia; however, not much research on this issue has been published since. In one published article, hypnotic analgesia was applied for burn injury treatment (1). The authors concluded that when all patients are included in the analysis, the hypnosis and control group did not differ in their posttreatment pain reports. However, when only patients with an intense baseline level of pain were considered, the hypnosis group reported experiencing significantly less posttreatment pain than did the control group after having adjusted for their baseline pain scores. In pain after Cesarean delivery, it has been reported that additive analgesic effect of codeine and paracetamol can be detected in strong, but not moderate, pain (2).

The third molar post-extraction pain model is a good acute analgesia model available at this time. The analgesic effect in this pain model has been reproducibly validated with the use of ibuprofen, other nonsteroidal antiinflammatory drugs, and by other analgesic medications (3). Moreover, this is a clean model, in the sense that by nature of the condition, participating subjects are relatively young and without other significant diseases that might be confounding factors in assessing analgesia. In addition, subjects consuming other analgesic drugs are excluded from these studies. Therefore, this dental pain model may generally be preferable for assessing factors that may potentially affect analgesic response. It has been reported that baseline pain intensity in the dental pain model was related to larger values for peak pain intensity differences, sum of pain intensity differences over time, and smaller values for the number of hours until remedication (3). However, it has also been reported that under the condition of a third molar surgical post-extraction, baseline pain was related to the degree of surgical trauma, but large interindividual variation in baseline pain intensity reduced the ability to distinguish between paracetamol with and without codeine (4). In a previous exploratory work, we showed that severe baseline pain in the third molar post-extraction dental pain situation was associated with better and more sustained pain intensity and pain relief scores after an ibuprofen 400 mg administration (5). However, this was based on two fairly small trials, and this trend, although very consistent, achieved statistical significance only at two hours after medication.

In this study, we performed a pooled raw data analysis. However, because of the homogeneity of the design of these studies, the analysis of the aggregated data may be regarded as equivalent to analysis of a multicenter study. The inclusion and exclusion criteria and the full study protocols were practically the same for all studies. The data collected were the raw data, the measurement tools for collecting end-points used in all studies were identical, and the quality of all the data met the FDA standards. In the analyzed studies, categorical scales were used for measuring pain. Averaging ordinal values is not a statistical procedure, but among analgesia investigators, this is the common practice for exhibiting dental pain results because of practical advantages regarding summary measures. Subjects with moderate baseline pain outnumber those with severe baseline pain (63% versus 37%, respectively, in our analysis) in our dental extraction studies.

In conclusion, this paper confirms our earlier exploratory work (5) that more severe baseline pain in the third molar post-extraction dental pain situation is associated with relatively greater decreasing of pain intensity scores after an ibuprofen 400 mg administration. However, more patients with less intense baseline pain were relieved by the medication. Patients with more baseline pain in the postoperative dental pain model may increase discrimination of analgesic properties of drugs. These data indicate that most people with severe initial pain do not require larger doses of analgesics. Studies in other pain models

should be performed to investigate the validity of these conclusions.

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